

## **REMARKS**

### **Amendments**

Claims 56-61, 64-68, 84-93, and 96-100 are currently pending in the application.

Claims 1-55 have been cancelled without prejudice or disclaimer solely to comply with the requirement to cancel the non-elected claims in the application. Applicants reserve the right to present the cancelled claims in a co-pending application.

Claims 56, 84, 92, 93, and 98 have been amended for clarity.

Specifically, claim 56 has been amended:

- to replace recitation of “nucleic acid disposed therein” with “nucleic acid therein;” and
- to replace the recitation “plurality of beads disposed within wells” with “plurality of beads within wells” (see, *inter alia*, page 31, lines 21-29).

Claim 84 has been amended:

- to replace recitation of “a nucleic acid disposed therein” with “a nucleic acid therein;”
- to replace recitation of “plurality of beads disposed within wells” with “plurality of beads within wells;”
- to replace recitation of “the nucleic acids disposed on beads in the wells” with “nucleic acids in the wells;” and
- to replace recitation of “delivering pyrophosphate sequencing reagents” with “delivering additional pyrophosphate sequencing reagents” (see, *inter alia*, page 31, lines 21-29).

Claims 92, 93, and 98 have been amended to replace recitation of “said sequencing reagent” with “said pyrophosphate sequencing reagent” (see, *inter alia*, page 31, lines 21-29).

Claim 100 has been added to more fully encompass Applicants’ invention. Claim 100 includes recitation of “nucleic acid is immobilized on the wells or on said beads” (see, *inter alia*, page 31, lines 21-29 and original claims 84-87 (discussed below)).

The paragraph on page 43, lines 16-21 has been amended to replace recitation of “http” with “hypertext transfer protocol,” which is the corresponding phrase for this acronym.

A new paragraph has been inserted on page 33, line 17 to include the subject matter disclosed in original claims 84-87 (discussed below).

These amendments are supported by the application as originally filed, and do not constitute new matter. Specific support for the amendments is shown in parentheses, above. Entry of these amendments is respectfully requested.

### **Priority**

The Examiner has stated that the claimed subject matter lacks support under 35 U.S.C. §112, first paragraph (Office Action, page 2). The Examiner has thereby concluded that the effective priority date for the instant application is the filing date of March 21, 2001 (Office Action, page 2). Applicants respectfully assert that the claims of the instant application are supported by the disclosure of priority document U.S. Application Serial No. 09/664,197, filed September 18, 2000. As illustration, Applicants point to the specific disclosure of Application Serial No. 09/664,197, as follows.

- Page 4, line 4 to page 7, line 23, discloses, *inter alia*, the cavitated fiber optic surface, the bundled fiber optic surfaces, apparatuses for sequence analysis, pyrophosphate sequencing reagents, linkage of nucleic acids to the support surface, the distance of the nucleic acids on the claimed substrate, the number of wells, and the sequencing of PCR products (discussed below).
- Figures 1-4 disclose, *inter alia*, the CCD and computer, the fiber optic substrate, and the wells of the fiber optic substrate;
- Page 8, line 5 to page 9, line 18, discloses, *inter alia*, linkage of nucleic acids to the substrate surface and the sequencing of PCR products (discussed below);
- Page 10, line 21 to page 15, line 6, discloses, *inter alia*, linkage of nucleic acids to the substrate surface;
- Page 24, line 9 to page 32, line 24, discloses, *inter alia*, pyrophosphate sequencing reagents (e.g., sulfurylase and luciferase), sequential addition of dNTPs, and the immobilization of sequencing reagents on beads;
- Page 32, line 26 to page 38, line 11, discloses, *inter alia*, the diameter of the individual fibers, the thickness of the wafer, the depth of the wells, the optional connection to a second fiber optic bundle, and the coating of the wafer;
- Examples 1 and 2 disclose, *inter alia*, the tandem amplification and sequencing of a nucleic acid on the same wafer surface;

- Original claims 59-62 include the same disclosure as original claims 84-87 of the instant application (discussed below).

Applicants note that the Examiner has not identified any specific subject matter of the claimed invention that allegedly lacks support in priority document U.S. Application Serial No. 09/664,197. In addition, the Examiner has not specified the individual claims that are alleged to lack such support. As listed above, Applicants have pointed to exemplary disclosure in priority document U.S. Application Serial No. 09/664,197 which provides support for the subject matter of the claims of instant application under 35 U.S.C. §112, first paragraph. It is respectfully asserted that the pending claims of the instant application are entitled to a priority date of September 18, 2000.

#### **Election/Restrictions**

The Examiner has required Applicants to cancel claims 1-55 of the instant application, as such claims are directed to non-elected subject matter (Office Action, page 2). Applicants have canceled claims 1-55 as a result of this Amendment, but reserve the right to present the cancelled claims in a co-pending application (see above).

#### **Information Disclosure Statements**

The Examiner has provided Applicants with a signed copy of the Modified Form PTO-1449 filed on February 1, 2002, as well as newly signed copies of the Modified Form PTO-1449 filed on June 12, 2003 and the Modified Form PTO-1449 filed on September 5, 2003 indicating consideration of all of the listed publications (Office Action, pages 2-3). Applicants acknowledge receipt of these papers in connection with the instant application.

#### **Specification**

The Examiner has objected to the specification for containing a hyperlink or other form of browser-executable code (Office Action, page 3). In particular, the Examiner pointed to the hyperlink on page 43, lines 20-21 of the instant application (Office Action, page 3). Applicants have amended the specification to deactivate the hyperlink (see above). Specifically, the acronym “http” has been replaced with the corresponding phrase “hypertext transfer protocol.” This amendment is supported by the original application, as filed, and constitutes no new matter

(see above). It is believed that deactivation of the hyperlink in the specification obviates this ground of objection, and reconsideration is respectfully requested.

### **Rejection under 35 U.S.C. §112, First Paragraph**

The Examiner has rejected claims 56-61, 64-68, 84-93, and 96-99 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement (Office Action, page 4). The Examiner states that the rejected claims contain new matter, i.e., subject matter which the Examiner has deemed not described in the specification in such a way to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, page 4). In particular, it is alleged that there is no support in the specification for the subject matter of 1) sequencing reagents immobilized on beads (Office Action, page 5); or 2) nucleic acids attached to beads (Office Action, page 6). Applicants respectfully traverse this rejection as follows.

#### **1. Support for Pyrophosphate Sequencing Reagents Attached to Beads**

Applicants respectfully assert that the instant application fully supports the claimed subject matter directed to sequencing reagents immobilized on beads. As presently amended, claims 56 and 84 recite the phrase “beads having a pyrophosphate sequencing reagent attached thereto.” In support of this recitation, Applicants have pointed to page 31, lines 21-29 of the originally filed specification, which states:

In various embodiments, some components of the reaction are immobilized, while other components are provided in solution. For example, in some embodiments, the enzymes utilized in the pyrophosphate sequencing reaction (e.g., sulfurylase, luciferase) may be immobilized if desired onto the solid support. Similarly, one or more of the enzymes utilized in the pyrophosphate sequencing reaction, e.g., sulfurylase, luciferase may be immobilized at the termini of a fiber optic reactor array. Other components of the reaction, e.g., a polymerase (such as Klenow fragment), nucleic acid template, and nucleotides can be added by flowing, spraying, or rolling. In still further embodiments, one more of the reagents used in the sequencing reactions is delivered on beads (Emphasis added).

When read in context, this paragraph describes various ways that the components of the sequencing reaction can be presented. According to this paragraph, a reaction component 1) can

be immobilized or provided in solution; 2) (an enzyme) can be immobilized on the solid support; 3) (an enzyme) can be immobilized at the array termini; 4) can be added by flowing, spraying, or rolling; or 5) can be delivered on beads.

In the Office Action, the Examiner states that use of the language “*delivered on beads*” indicates that the reagents are specifically *not* immobilized on the beads (Office Action, page 5). Yet, the phrase “delivered on” is commonly used in scientific publications to refer to delivery via an attachment or linkage. Applicants point to Exhibits 1-7, attached hereto. In particular:

- Rhoades et al., 2003, *Mol. Microbiol.* 48:875-888 (Exhibit 1) explicitly refers to BCG lipids “delivered on” polystyrene microspheres (see, *inter alia*, summary; page 881, left column; and page 884, left column);
- Sedegah et al., 2000, *J. Immunol.* 164:5905-5912 (Exhibit 2) explicitly refers to DNA “delivered on” gold particles (see, *inter alia*, page 5911, left column);
- Leister et al., 1996, *Proc. Natl. Acad. Sci. USA* 93:15497-15502 (Exhibit 3) explicitly refers to a LUC reporter gene “delivered on” biolistic particles (see, *inter alia*, page 15501, right column);
- Bowes et al., 2002, *Infect. Immun.* 70:5008-5018 (Exhibit 4) explicitly refers to a GD3 ganglioside “delivered on” lipopolysaccharides (see, *inter alia*, page 5013, bottom right column to page 5014, top left column);
- Reeves et al., 2002, *J. Biol. Chem.* 277:9155-9159 (Exhibit 5) explicitly refers to a replacement cassette “delivered on” a KC515 phage vector (see, *inter alia*, page 9157, legend for Figure 2);
- Legge et al., 1997, *J. Exp. Med.* 185:1043-1053 (Exhibit 6) explicitly refers to a PLP-LR peptide “delivered on” an Ig chimera (see, *inter alia*, page 1050, bottom left column to top right column); and
- Burton and Gray, 1995, *Br. J. Cancer* 71:322-325 (Exhibit 7) explicitly refers to radiation doses “delivered on” microspheres (see, *inter alia*, summary and page 323, top left column).

In each of these articles, the authors have employed the phrase “delivered on” to mean “delivery of ‘X’ via attachment or linkage to ‘Y’.” In view of this common usage, it is clear that “one or more of the reagents...is *delivered on beads*,” means “one or more of the reagents...is delivered *via attachment or linkage to beads*” as disclosed in the originally filed specification.

The Examiner argues that Applicants do not repeat the disclosure of page 31 (“one more of the reagents used in the sequencing reactions is delivered on beads”) elsewhere in the

specification. However, Applicants are not required to repeat a disclosure throughout the instant application. Further, Applicants respectfully submit that the Examiner's interpretation of the specification would lead to an illogical result.

If the Examiner's interpretation were accepted, then *none* of the key components of the reaction could be deemed attached to beads, since the Examiner argues that the specification fails to support *either* sequencing reagents immobilized on beads (Office Action, page 5) *or* nucleic acids attached to beads (Office Action, page 6). This is clearly an erroneous outcome given the disclosure on page 31, lines 21-29 of the instant application (excerpted above). Applicants respectfully submit that the originally filed specification fully supports claims 56 and 84, which recite "beads having a pyrophosphate sequencing reagent attached thereto."

## 2. Support for Nucleic Acids Attached to Beads

Applicants respectfully assert that the instant application fully supports the claimed subject matter directed to nucleic acids attached to beads. As presented herein:

- Claim 57 recites "nucleic acid is immobilized on the wells or on said beads;"
- Claim 67 recites "nucleic acid sequences are attached to the wells or beads;"
- Claim 68 recites "nucleic acid sequences are...attached to the wells or beads;" and
- New claim 100 recites "nucleic acid is immobilized on the wells or on said beads."

For clarity, independent claim 84 has been amended to delete the recitation "the nucleic acids disposed on beads" (see above).

The Examiner states that the application teaches *only* that biotin-avidin binding can be used to immobilize nucleic acids to the reaction wells of the apparatus (Office Action, pages 5-6). Yet, Applicants point to page 39, lines 21-22 of the originally filed specification, which indicates that previous experiments had shown that PCR products were capable of being conjugated to streptavidin-coated magnetic beads.

In addition, the Examiner states that disclosure of "nucleic acids attached to beads" is nowhere to be found in the application (Office Action, page 5). Yet, Applicants point to page 31, lines 21-29 of the originally filed specification (excerpted above), and to original claims 84-87, which state:

84. An apparatus for processing a plurality of analytes, the apparatus comprising:

a flow chamber having disposed therein a substrate comprising a plurality of cavitated surfaces, said cavitated surfaces having disposed thereon nucleic acid molecules;

fluid means for delivering processing reagents from one or more reservoirs to the flow chamber so that the analytes anchored to the plurality of microparticles are exposed to the reagents; and

detection means for detecting a sequence of optical signals from each microparticle of the plurality, each optical signal of the sequence being indicative of an interaction between a processing reagent and the analyte anchored thereto, wherein said detection means is in communication with the cavitated surfaces.

85. The apparatus of claim 85, wherein said detection means further comprises signal tracking means for correlating said optical signals from each of said microparticles in each of said digital images to form for each said microparticle of said plurality a sequence of said optical signals.

86. The apparatus of claim 87, wherein said signal tracking means is a CCD camera.

87. The apparatus of claim 86, wherein said analyte is DNA. (Emphasis added).

These original claims describe various features of the sequencing apparatus, including cavitated surfaces (wells) with nucleic acids (e.g., DNA) anchored to microparticles (beads). As a result of this amendment, Applicants have incorporated original claims 84-87 in paragraph form in the specification (see above). The added paragraph does not constitute new matter, since the claims as filed in the original specification are part of the disclosure (MPEP §2163.06(III)). Moreover, the specification may be amended to include the subject matter of an originally filed claim (MPEP §2163.06(III)).

In addition, Applicants note that mere rephrasing of a passage does not constitute new matter (MPEP §2163.07(I)). As seen in scientific publications, the terms “microparticles” and “beads” are used interchangeably. Applicants point to Exhibits 8-13, attached hereto:

- Schweitzer et al., 2000, *Proc. Natl. Acad. Sci. USA* 97:10113-10119 (Exhibit 8; see, *inter alia*, page 10114, right column and page 10116, right column);
- Spiro et al., 2002, *Appl. Environ. Microbiol.* 68:1010-1013 (Exhibit 9; see, *inter alia*, page 1010, right column and page 1012, right column);

- Borowitz et al., 1997, *Blood* 89:3960-3966 (Exhibit 10; see, *inter alia*, page 3960, right column);
- Simone et al., 1999, *Am. J. Pathol.* 156:445-452 (Exhibit 11; see, *inter alia*, page 446, right column);
- Chen et al., 1999, *Clin. Chem.* 45:1693-1694 (Exhibit 12; see, *inter alia*, page 1693, right column and page 1694, right column); and
- de Bruin et al., 2000, *J. Gen. Virol.* 81:1529-1537 (Exhibit 13; see, *inter alia*, page 1532, left column).

Applicants respectfully submit that the originally filed application supports claims 57, 67, 68, and new claim 100, which recite “nucleic acid...immobilized on the wells or on said beads” or “nucleic acid sequences...attached to the wells or beads.”

In view of all of the foregoing, Applicants conclude that independent claims 56 and 84 and corresponding dependent claims 57-61, 64-68, 84-87, 88-93, 96-100 do not contain new matter. Withdrawal of this rejection is respectfully requested.

### 3. **Telephone Interview Regarding Rejection under 35 U.S.C. §112, First Paragraph**

On November 19, 2003, Applicants’ undersigned attorney and agent initiated a telephone interview with the Examiner to ask for clarification regarding the rejection set forth under 35 U.S.C. §112, first paragraph. The Examiner stated that it was unclear as to whether claims 56 and 84 included limitations for beads that were simultaneously attached to substrate and pyrophosphate sequencing reagents. The Examiner asked that the claims be amended to clarify this issue. Applicants’ undersigned attorney and agent agreed to make amendments to claims 56 and 84 for clarity. As indicated above, claims 56 and 84 have been amended to change the recitation of “beads disposed within wells” to “beads within wells.” While the term “disposed” is not limited by its usage in the instant application to mean “attached,” Applicants wish to provide clarification as required by the Examiner. Withdrawal of the new matter rejection is therefore respectfully requested.

### **Rejection under 35 U.S.C. §112, Second Paragraph**

The Examiner has rejected claims 84, 85-87, 92, 93, 96-99 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the

subject matter Applicants' regard as the invention (Office Action, page 6). The Examiner has stated:

- In claim 84, the phrase "the nucleic acid disposed on beads" lacks antecedent basis; and
- In claims 92, 93, and 98, the phrase "said sequencing reagent" lacks antecedent basis.

Applicants have amended claims 84, 92, 93, and 98 for clarity. Specifically:

- In claim 84, the phrase "the nucleic acids disposed on beads" has been amended to read "nucleic acids in the wells;" and
- In claims 92, 93, and 98, the phrase "said sequencing reagent" has been amended to read "said pyrophosphate sequencing reagent."

These amendments are supported by the application as originally filed, and do not constitute new matter. It is believed that the amendments obviate this ground of rejection. Withdrawal of the rejection is respectfully requested.

#### **Rejection under 35 U.S.C. § 103(a)**

The Examiner has newly rejected claims 56-61, 64-68, 84-93, and 96-99 under 35 U.S.C. §103(a) as allegedly unpatentable over Chee et al. (U.S. Published Application No. 2003/1018867 ("Chee et al."); Office Action, page 7). The Examiner states that Chee et al. describe a substrate for pyrophosphate sequencing and an apparatus for the substrate. The Examiner notes that Chee et al. fail to teach: 1) imaging through a CCD (charged coupled device); 2) the diameter of the individual optic fiber or the depth of the cavitated fiber optic wafer; 3) various separation distances between the nucleic acids on the substrate/apparatus; and 4) an optical linkage between the polished end of the fiber optic wafer and a second fiber optic fiber (Office Action, page 9). However, the Examiner states that it would have been obvious to one of skill in the art to modify the teachings of Chee et al. to arrive at the invention as claimed (Office Action, page 9). Applicants respectfully traverse this rejection as follows.

#### **1. *Chee et al.* do not teach or suggest the coating limitations of the instant claims**

The Examiner states that Chee et al. expressly disclose the use of "photolithography" (paragraphs [0111] – [0114]) and thereby teach the subject matter of instant claims 90, 91, 96,

and 97 (Office Action, page 8). However, paragraphs [0111] – [0114] of Chee et al. do not contain the express teaching of instant claims 90, 91, 96, and 97, which recite:

90. The substrate of claim 56 wherein the cavitated fiber optic wafer is coated.

91. The substrate of claim 90 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and pluronic polymers.

96. The apparatus of claim 84 wherein the cavitated fiber optic wafer is coated.

97. The apparatus of claim 96 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and pluronic polymers (emphasis added).

Specifically, paragraphs [0111] – [0114] of Chee et al. do not teach or suggest cavitated fiber optic wafers which comprise a “coating,” including a “plastic coating,” or a coating of “gold layer,” “organosilane reagents,” “photoreactive linkers,” “hydrophilic polymer gels,” or “pluronic polymers.” Paragraph [0114] of Chee et al. refers only to the use of “chemically modified sites” (paragraph [0114]). Thus, Chee et al. do not teach or suggest the subject matter of instant claims 90, 91, 96, and 97. MPEP 2142 states that for a *prima facie* case of obvious, a prior art reference must teach or suggest all the claim limitations. In addition, there must be a suggestion or motivation in the reference to modify the prior art to obtain the claimed invention. MPEP §2143.01 (see below). Here, neither requirement has been met. Therefore, it is respectfully asserted that instant claims 90, 91, 96, and 97 are not unpatentable over Chee et al. as cited by the Examiner.

**2. Chee et al. do not teach or suggest the separation limitations of the instant claims**

The Examiner states that Chee et al. expressly disclose “high density” arrays (paragraph [0105]) and thereby make obvious the subject matter of instant claims 59-61 (Office Action, page 8). However, paragraph [0105] of Chee et al. refers to arrays containing 40,000 beads/mm<sup>2</sup> to 1,000,000 beads/mm<sup>2</sup> (Office Action, pages 9-10). This corresponds to 40 beads/μm<sup>2</sup> to 1000 beads/μm<sup>2</sup>, meaning that each bead would be separated by approximately 0.17 μm to 0.03 μm (see Declaration of Dr. Margulies under 37 C.F.R. §1.132, attached hereto).

In contrast, the instant claims recite:

59. The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 10  $\mu$ m to approximately 200  $\mu$ m.

60. The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 10  $\mu$ m to approximately 150  $\mu$ m.

61. The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 150  $\mu$ m (emphasis added).

Accordingly, paragraph [0105] of Chee et al. does not teach or suggest fiber optic surfaces which comprise a “nucleic acids” that are separated by “approximately 10  $\mu$ m to approximately 200  $\mu$ m,” “approximately 10  $\mu$ m to approximately 150  $\mu$ m,” or “approximately 150  $\mu$ m.” Thus, Chee et al. paragraph [0105] does not teach or suggest the subject matter of instant claims 59-61. MPEP 2142 states that for a *prima facie* case of obvious, a prior art reference must teach or suggest all the claim limitations. In addition, there must be a suggestion or motivation in the reference to modify the prior art to obtain the claimed invention. MPEP §2143.01 (see below). Here, neither requirement has been met. Therefore, it is respectfully asserted that instant claims 59-61 are not unpatentable over Chee et al. as cited by the Examiner.

3. **Chee et al. do not teach or suggest the compact wafer, detachable fiber, optic linkage, flow chamber, or fluid means of the instant claims**

The Examiner states that Chee et al. fail to disclose the specific compact wafer, detachable fiber, and optical linkage recited in the instant claims (Office Action, page 9). Applicants add that Chee et al. also fail to disclose the specific flow chamber and fluid means recited in the claims. The Examiner states that that the compact wafer of the invention is merely ornamental and imparts no mechanical function (Office Action, page 10). Applicants respectfully emphasize that the recited compact wafer, detachable fiber, optical linkage, flow chamber, and fluid means impart notable *functional* advantages over the Chee et al. fiber, and other sequencing systems (see Dr. Margulies’ Declaration, ¶¶ 5-14).

The substrate of instant claims includes a compact wafer between 0.5 mm and 5.0 mm in thickness (see, *inter alia*, page 36, lines 12-15; and page 36, line 30 to page 37, line 3). The instant application teaches that the wafer can be fit into a flow chamber and fluid means for delivering sequencing reagents and washes to the wafer surface (see, *inter alia*, Figures 2 and 3; page 4, lines 14-18; page 30, lines 15-19; page 33, line 20 to page 35, line 20; and Example 3 on page 53, line 28 to page 54, line 15). For sequence analysis, the underside of the claimed compact wafer in the flow chamber can be optically linked or directly contacted with a second optical fiber to allow image capture, for example, through a CCD system (see, *inter alia*, page 34, lines 13-18; and Figure 2). Alternatively, the underside of the compact wafer in the flow chamber can be placed in proximity to conventional optics mechanism, e.g., a high numerical aperture lens system to allow for image capture (see, *inter alia*, page 34, lines 19-23).

Due to the recited wafer size, flow chamber, fluid means, detachable fiber, and optical linkage the claimed substrate and apparatus yield significantly improved results compared to the system of Chee et al. (Dr. Margulies' Declaration, ¶ 10). The compact wafer of the invention is suitable for use flow chambers and fluid means, while the Chee et al. fibers are not (Dr. Margulies' Declaration, ¶¶ 10-11). Chee et al. (paragraph [0007], relying on WO 98/50782) are limited to the use of optical fibers extending several meters (see Dr. Margulies' Declaration, ¶ 11; WO 98/50782 page 14, lines 18-20).<sup>1</sup> The Chee et al. fibers are excessively long and therefore not compatible for use with flow chambers and fluid means (Dr. Margulies' Declaration, ¶ 11). Instead, Chee et al. report the use of a "dipping" mechanism, which involves inverting the long optical fiber and sequentially dipping the tip into individual cups filled with solutions of single nucleotides (Chee et al., ¶¶ [0192] – [0195], *inter alia*; Dr. Margulies' Declaration, ¶ 11).

The dipping mechanism of Chee et al. appears inoperable, or at best, unwieldy and inefficient for sequence analysis (Dr. Margulies' Declaration, ¶¶ 12-13). In contrast, the compact wafer of the invention can be placed into a flow chamber with fluid means to provide rapid and efficient delivery of sequencing reagents and washes (Dr. Margulies' Declaration, ¶¶ 13-14). Thus, the claimed wafer, detachable fiber, and optical linkage (and flow chamber with fluid means) are *not merely aspects of ornamentation*, but rather, highly advantageous *functional* features of Applicants' invention (Dr. Margulies' Declaration, ¶¶ 5 and 14).

---

<sup>1</sup> WO 98/50782 was submitted with Applicants' Information Disclosure Statement mailed February 1, 2002.

Thus, Chee et al. do not teach or suggest the subject matter of instant claims 56-61, 64-68, 84-93, and 96-99, including the recited compact wafer, detachable fiber, optical linkage, nucleic acid separation, flow chamber, and fluid means. MPEP 2142 states that for a *prima facie* case of obvious, a prior art reference must teach or suggest all the claim limitations. In addition, there must be a suggestion or motivation in the reference to modify the prior art to obtain the claimed invention. MPEP §2143.01 (see below). Here, neither has been shown by the Examiner. Moreover, the recited features of claims 56-61, 64-68, 84-93, and 96-99 are not merely “ornamentation.” Rather, these features impart functional advantages over the system of Chee et al. and others (Dr. Margulies’ Declaration, ¶¶ 5 and 14). Therefore, it is respectfully asserted that instant claims 56-61, 64-68, 84-93, and 96-99 are not unpatentable over Chee et al. as cited by the Examiner.

4. **The compact wafer, detachable fiber, and optic linkage of the instant claims are not equivalent to the fiber of *Chee et al.***

The Examiner states that because the claimed wafer *can* be attached to a second optical fiber bundle to transmit data to an imaging device, Applicants’ invention is tantamount to the fiber of Chee et al. (Office Action, page 10). However, the instant application discloses that the second optical fiber bundle may be optically linked with the compact wafer (see, *inter alia*, page 34, lines 13-14; see also current claim 89). Thus, the light generated by the compact wafer can be transmitted to the exterior of the flow chamber to allow signal detection (see, *inter alia*, page 34, lines 13-18; and Figure 2).

Due to this detachable fiber and optical linkage, the compact wafer can be used in a flow chamber to allow rapid and efficient delivery of sequencing reagents and washes (Dr. Margulies’ Declaration, ¶ 10). By comparison, Chee et al. are limited to the use of long, bulky fibers that necessitate a slow, inefficient, and wasteful “invert and dip” mechanism (Dr. Margulies’ Declaration, ¶ 11). Therefore, the claimed wafer, detachable fiber, and optical linkage are not equivalent to the extended fibers of Chee et al. as cited by the Examiner.

5. **Chee et al. do not teach or suggest the specific dimensions of the compact wafer as recited in the instant claims**

The Examiner states that Chee et al. fail to disclose the specific diameter of the optical fibers of the compact wafer recited in the instant claims (Office Action, page 9). Applicants add that Chee et al. also fail to disclose the specific depths of the wells of the compact wafer recited in the claims. Applicants respectfully emphasize that these features impart notable *functional* advantages over the Chee et al. system (Dr. Margulies' Declaration, ¶¶ 15-30).

The substrate of instant claims includes a compact wafer between 0.5 mm and 5.0 mm in thickness (see, *inter alia*, page 36, lines 12-15; and page 36, line 30 to page 37, line 3). Additionally, the compact wafer includes optical fibers with a recited diameter of 3 mm to 100 mm (see, *inter alia*, page 36, line 15). The instant application teaches that this diameter is important to ensure that each light signal can be captured as a single pixel (see, *inter alia*, page 36, line 15 and 25-29). The compact wafer also includes wells with a recited depth of one-half to three times the diameter of the optical fibers (see, *inter alia*, page 37, lines 6-9). Relevant to this, the application expressly recognizes the problem of bead/sample loss during the sequencing reaction (see, *inter alia*, page 37, lines 6-9; page 39, lines 22-24; and Figure 4).

Due to the recited fiber diameter and well depth, the claimed substrate and apparatus yield significantly improved results compared to the system of Chee et al. (Dr. Margulies' Declaration, ¶ 18). Many of the fibers reported by Chee et al. are not useful for sequence analysis due to their excessively small size (Dr. Margulies' Declaration, ¶ 20). Chee et al. paragraph [0105] suggests the use of "high density" long optical fibers with diameters ranging from 0.17  $\mu\text{m}$  to 0.03  $\mu\text{m}$  (Dr. Margulies' Declaration, ¶ 19). These dimensions can be calculated from the range of optical fiber densities indicated by Chee et al. paragraph [0105], i.e., arrays containing 40,000 fibers/ $\text{mm}^2$  to 1,000,000 fibers/ $\text{mm}^2$  (Chee et al., ¶ [0105]; Dr. Margulies' Declaration, ¶ 19).

With diameters of approximately 0.17  $\mu\text{m}$  to 0.03  $\mu\text{m}$ , many of the optical fibers employed by Chee et al. produce sequencing systems that are completely or partly inoperable (see Dr. Margulies' Declaration, ¶ 20). For example, such systems would have problems in distinguishing light signals from each fiber and in depositing the beads in the wells (Dr. Margulies' Declaration, ¶ 20). In comparison to Chee et al. paragraph [0105], the compact wafer of the invention employs optical fibers 3  $\mu\text{m}$  to 100  $\mu\text{m}$  in diameter to provide for maximal

sample density while still allowing accurate signal detection and efficient bead delivery (Dr. Margulies' Declaration, ¶ 20).

The wells reported by Chee et al. do not appear to have any specified depth, suggesting that that Chee et al. have failed to recognize the importance of well depth in preventing sample loss. Figure 1 in Chee et al. shows beads and samples jutting out from their wells, which would seem to lead to significant sample loss during their "invert and dip" process (see Dr. Margulies' Declaration ¶ 21). In contrast, the compact wafer of the invention employs well depths of one-half to three times the diameter of the fiber to help minimize sample loss during preparation and analysis (see Dr. Margulies' Declaration, ¶ 21). The claimed dimensions of the fibers and wells therefore represent significant *functional advantages* over the system reported in Chee et al.

Thus, as cited by the Examiner, Chee et al. do not teach or suggest the subject matter of instant claims 56-61, 64-68, 84-93, and 96-99, including the including the recited compact wafer, fiber diameter, and well depth. MPEP 2142 states that for a *prima facie* case of obvious, a prior art reference must teach or suggest all the claim limitations. In addition, there must be a suggestion or motivation in the reference to modify the prior art to obtain the claimed invention. MPEP §2143.01 (see below). Here, neither has been shown by the Examiner. Moreover, the recited features of claims 56-61, 64-68, 84-93, and 96-99 represent functional advantages in view of Chee et al. (Dr. Margulies' Declaration, ¶ 21). Therefore, it is respectfully asserted that instant claims 56-61, 64-68, 84-93, and 96-99 are not unpatentable over Chee et al. as cited by the Examiner.

**6. Conclusion: the instant claims are not obvious in view of *Chee et al.* as cited by the Examiner**

First, the Examiner states that Chee et al. fail to teach a cavitated fiber comprising a depth between 0.5 mm and 5.0 mm, but alleges that the compact wafer is obvious since it imparts only ornamentation and no mechanical function (Office Action, pages 10-11). Yet, Applicants have demonstrated that the wafer element of the instant application imparts notable *functional advantages* over the Chee et al. system and others (Dr. Margulies' Declaration, ¶¶ 5-14 and 15-21).

Applicants' recognize that, in some cases, the particular shape of a product is considered to lack patentable significance. MPEP § 2144.04; *Ex parte Hilton*, 148 USPQ 356 (Bd. App.

1965). However, the shape and size of the claimed wafer element, along with the detachable linkage, flow chamber and fluid means, fiber diameter, and well depth impart patentable significance, since these features results in substrates and apparatuses that are clearly distinct from and superior to other sequencing platforms, including that of Chee et al. (Dr. Margulies' Declaration, ¶¶ 10 and 18). See MPEP § 2144.04; *Ex parte Hilton*, 148 USPQ 356 (Bd. App. 1965).

The claimed invention, which includes the compact wafer and the other functional features, has been shown to outperform other sequencing devices and to allow whole-genome sequencing (Dr. Margulies' Declaration, ¶¶ 22-30). The Examiner is required to consider these inherent advantages, properties, utilities, and results flowing from the claimed invention, since each is a part of the invention as a whole. *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987); *Fromson v. Advance Offset Plate*, 755 F.2d 1549 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984); *Carl Schenck, AG v. Nortron Corp.*, 713 F.2d 782 (Fed. Cir. 1983); *In re Sernaker*, 702 F.2d 989 (Fed. Cir. 1983).

Second, the Examiner states that Chee et al. fail to teach numerous recited features of the claimed substrate and apparatus, including the compact wafer, fiber diameter, well depth, nucleic acid separation, optical linkage, and detachable optical fiber (Office Action, page 9). Applicants add that Chee et al. also fail to teach the recited flow chamber, fluid means, and well depth. However, the Examiner states that it is well within the purview of an ordinarily skilled artisan to make modifications to the system of Chee et al. and arrive at the invention as claimed (Office Action, page 9). It is further stated that modification of the Chee et al. system to obtain claimed invention would yield a reasonable expectation of success (Office Action, pages 9-10).

Yet, Applicants note that “although a prior art device may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so” in order to establish obviousness. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990) (emphasis added). The fact that the claimed invention is alleged to be within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case under Section 103. MPEP §2143.01; *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

Here, the Examiner has failed to provide any suggestion or motivation to modify the substrate of Chee et al. to obtain the *specifically claimed features* of the compact wafer, flow chamber, fluid means, fiber diameter, well depth, nucleic acid separation, detachable optical

fiber, and optical linkage of Applicants' invention. The Examiner relies on the "high density" arrays of Chee et al. paragraph [105] to allegedly show that the claimed separation distances between the nucleic acids is within the purview of a person in the art (Office Action, page 10). Yet, the high density arrays of Chee et al. correspond to separation distances of approximately 0.17  $\mu\text{m}$  to 0.03  $\mu\text{m}$  (Dr. Margulies' Declaration, ¶ 19). In contrast, the instant claims recite distances of "approximately 10  $\mu\text{m}$  to approximately 200  $\mu\text{m}$ ," "approximately 10  $\mu\text{m}$  to approximately 150  $\mu\text{m}$ ," or "approximately 150  $\mu\text{m}$ ." The Examiner provides no suggestion or motivation in Chee et al. paragraph [105] to employ the *specifically recited* distances. Moreover, the Examiner provides no suggestion or motivation in any part of Chee et al. to arrive at the specifically recited features of the compact wafer, flow chamber, fluid means, fiber diameter, well depth, optical linkage, and detachable optical fiber of the instant claims.

Thus, it is respectfully submitted that a *prima facie* case of obviousness has not been established against the instant claims. In view of all of the above, Applicants respectfully submit that claims 56-61, 64-68, 84-93, and 96-99 (as well as new claim 100) are not unpatentable over Chee et al. as cited by the Examiner. Reconsideration of the pending claims is respectfully requested.

**Declaration under 37 C.F.R. §1.132 from Marcel Margulies filed October 9, 2003**

In the Office Action, the Examiner failed to considered the Rule 132 Declaration of Dr. Marcel Margulies, which was filed in the U.S. Patent and Trademark Office on October 9, 2003 (see stamped Transmittal Letter and Declaration (page 1); Exhibit 14). Applicants' have resubmitted the contents of this Declaration in the new Rule 132 Declaration submitted herewith. Entry and consideration of the newly filed Rule 132 Declaration of Dr. Margulies is respectfully requested.

**CONCLUSION**

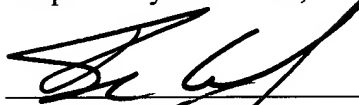
Applicants believe that the claims as amended are patentable and a prompt allowance is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance. While Applicants believe that no additional fees are required, the Commissioner is authorized to charge or credit the undersigned

Applicants: Rothberg, et al.  
U.S.S.N. 09/814,338

Deposit Account No. 50-0311, Reference No. 21465-501 CIP2, Customer No. 35437, for any additional fees needed.

Dated: April 23, 2004

Respectfully submitted,



Ivor Elrifi, Reg. No. 39,529  
Caryn DeHoratius, Reg. No. 45,881  
MINTZ, LEVIN, COHN, FERRIS,  
GLOVSKY and POPEO, P.C.  
The Chrysler Center  
666 Third Avenue, 24<sup>th</sup> Floor  
New York, NY 10017  
Tel: (212) 935-3000  
Fax: (212) 983-3115